Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 927–929
Tetrahedron Letters

An iodocyclisation/elimination approach to a DEF-ring core of FR182877

Paul A. Clarke,[a,*] Matthew Grist[a] and Mark Ebden[b]

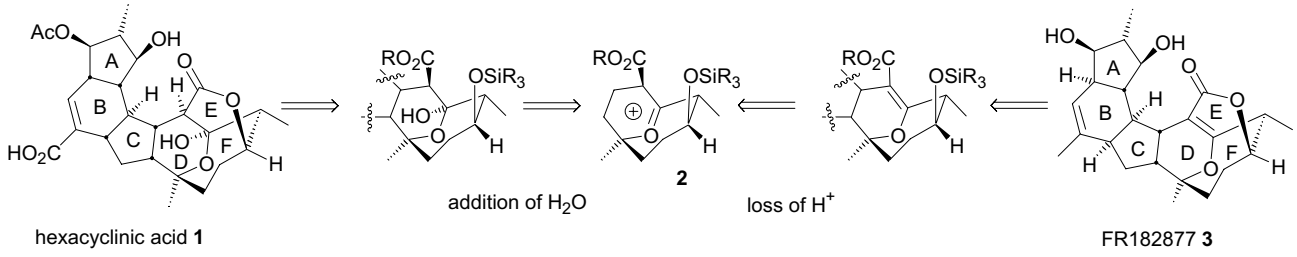
[a]School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK
[b]Medicinal Chemistry, AstraZeneca Charnwood, Bakewell Road, Loughborough LE11 5RH, Leics, UK

Received 31 October 2003; revised 14 November 2003; accepted 21 November 2003

Abstract—A transannular iodocyclisation reaction has directly furnished the DEF-ring system of the natural product FR182877. However, higher yields of the DEF-ring system are obtained via transannular iodocyclisation followed by elimination of acetic acid.

Hexacyclinic acid **1** and FR182877 **3** (Scheme 1) are two structurally related hexacyclic polyketide natural products, which have been shown to have anti-tumour activity.[1–4] Due to its unique vinylogous carbonate DEF-ring unit and greater activity, FR182877 has received the most attention from synthetic chemists. Several reports have appeared detailing synthetic endeavors towards FR182877's ring systems,[5–8] to date the most notable of which are the two total syntheses of FR182877 by both the groups of Sorensen[9] and Evans.[10] In contrast, there has been very little synthetic activity in the area of the synthesis of hexacyclinic acid. Recently, however, we completed studies which have resulted in the first-reported synthesis of the DEF-ring system of hexacyclinic acid utilising a transannular iodocyclisation strategy.[11] The structural similarities between hexacyclinic acid **1** and FR182877 **3** suggest that they may arise from the same biogenetic precursors and have similar biosyntheses. We wished to investigate the possibility that the DEF rings of hexacyclinic acid **1** and FR182877 **3** could be synthesised from a common synthetic precursor.

We reasoned that it may be possible to access the FR182877 DEF-ring system from the same oxocarbenium ion intermediate **2**, which leads to the formation of the hexacyclinic acid DEF-ring system (Scheme 1). In this strategy, the formation of the DEF-ring system of hexacyclinic acid requires addition of an oxygen nucleophile to oxocarbenium ion **2**, while the formation



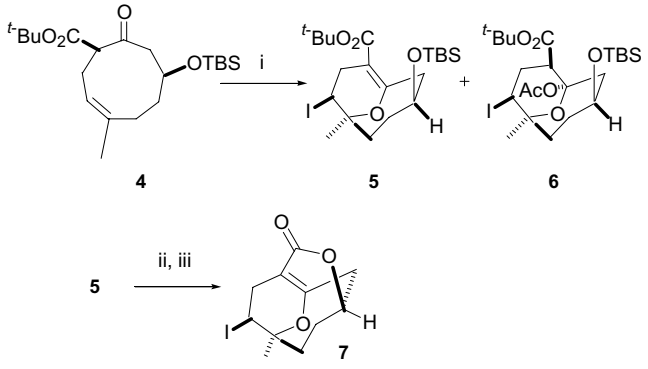
Scheme 1.

* Corresponding author. Fax: +44-115-951354; e-mail: paul.clarke@nottingham.ac.uk

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.105

of the DEF-ring system of FR182877 requires the loss of a proton from **2**.

The result which provided us with proof of this concept came when we repeated our previous synthesis of the DEF rings of hexacyclinic acid on a larger scale. Iodocyclisation precursor **4** was synthesised according to our previously published procedure.[11] Upon treatment of **4** with acetyl hypoiodite, we were able to isolate cyclic vinylogous carbonate **5** (5%), which corresponds to the DF-ring functionality of FR182877 in addition to the corresponding DF-ring system of hexacyclinic acid **6** (61%) (Scheme 2). The synthesis of a DEF-ring system of FR182877 **7** was completed by treatment of **5** with 40% aq HF in MeCN (100% yield), followed by quantitative removal of the *tert*-butyl ester and in situ lactonisation with TFA in CH_2Cl_2.



Scheme 2. Reagents and conditions: (i) AcOI, AcOH, (**5**) 5% and (**6**) 61%; (ii) 40% HF, MeCN, 100%; (iii) TFA, CH_2Cl_2, 100%.

Encouraged by this result, we attempted to bias the reaction to produce the FR182877 DF-ring system as the major product rather than the hexacyclinic acid one. However, despite many attempts we were unable to find conditions to do this. We decided that this was probably due to the nucleophilic nature of the acetic acid solvent, trapping the oxocarbenium ion at a rate faster than that of the desired loss of a proton. In an attempt to obviate this, we conducted transannular iodocyclisation studies in a series of non-nucleophilic solvents. As we have previously reported, when the iodocyclisation was carried out in $CHCl_3$ lactone **8** was formed.[11] When the reaction was carried out in Et_2O, however, yet another mode of cyclisation dominated. In this instance, iodocyclisation occurred via the oxygen of the silyl ether to generate [5.2.1] oxo-bicyclic ketone **9**. This presumably arises as the cyclisation occurs via the oxygen of the silyl ether through a boat–boat conformation of the nine-membered ring α-iodonium ion (Fig. 1). This cyclisation liberated an equivalent of TBSI, which promoted removal of the *tert*-butyl ester and subsequent decarboxylation. The related bicyclic compound **10**, in which the ester unit is intact, was isolated when THF, MeCN or MeOH were used as solvents. The use of other solvents (DMF, DMSO, benzene, EtOAc, hexane, CCl_4, TFA, pyridine or 1,1,1,3,3,3-hexafluoro-*iso*-propanol) resulted in no reaction taking place.

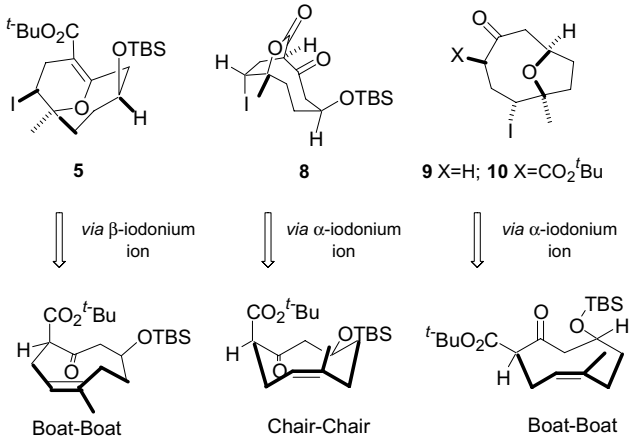
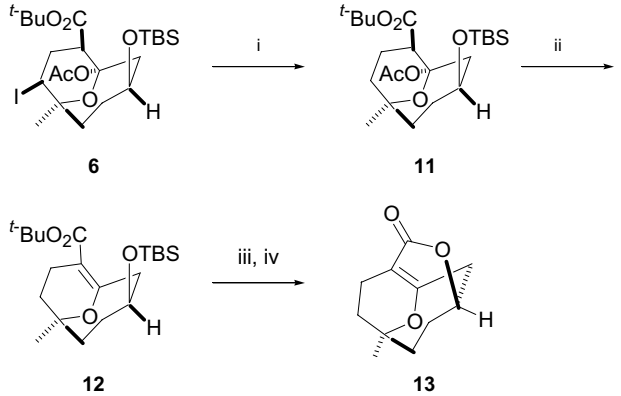


Figure 1.

From these studies it is clear that the nature of the solvent plays a crucial role in determining which mode of cyclisation dominates in any given reaction. As far as we are able to tell, the nine-membered ring **4** does not epimerise or enolise to any detectable extent in these reaction solvents. As all of the products **5**, **8** and **9/10** arise from the cyclisation of different oxygens onto different iodonium ions (either α- or β-) through different conformations (Fig. 1), we can only conclude at present that the solvent in some way stabilises one of these iodonium ion conformations with respect to the other possible iodonium ion conformations and that this governs which of the products is formed.

As we were unable to influence the course of the iodocyclisation reaction to provide access to greater quantities of **5** we sought to develop a route to convert **6** into a FR182877 DEF-ring system (Scheme 3). This was achieved by the reductive removal of the iodine, either via Bu_3SnH and catalytic AIBN or via catalytic transfer hydrogenation. The dehalogenated DF-ring **11** was treated with DBU,[12] which provided 56% yield of **12** at 56% conversion after 15 days. The DF-ring **12**, now contained the vinylogous carbonate unit required for the construction of the DEF rings of FR182877. The syn-



Scheme 3. Reagents and conditions: (i) $Pd(PPh_3)_4$, Bu_3N, HCO_2H, DMF, 23%; (ii) DBU, MeCN, reflux, 56%; (iii) 40% aq HF, MeCN, 100%; (iv) TFA, CH_2Cl_2, 100%.

thesis of a FR182877 DEF-ring **13** was achieved by deprotection and lactonisation by sequential treatment of **12** with aq HF in MeCN followed by TFA in CH_2Cl_2 in 100% yield over the two steps (Scheme 3).

In conclusion, we have shown that it is possible to access the DEF-ring systems of both hexacyclinic acid **1** and FR182877 **3** from a common oxocarbenium ion intermediate **2**, and we believe that this provides support for an alternative biosynthetic hypothesis to the one previously advanced.[8–10] However, we were able to obtain greater yields of a FR182877 ring system by combining the iodocyclisation event with an elimination reaction. Work is ongoing in an attempt to increase the efficiency of the iodocyclisation approach for the synthesis of FR182877 ring systems.

Acknowledgements

We thank the EPSRC and AstraZeneca for studentship funding under the CASE for New Academics Scheme and AstraZeneca for an unrestricted research support grant. We also acknowledge the EPSRC National Mass Spectrometry Service, Swansea for Mass Spec. determinations.

References and notes

1. Hofs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258.
2. Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123.
3. Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204.
4. Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.
5. Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron Lett.* **2002**, *43*, 2753.
6. Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585.
7. Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263.
8. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645; Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307.
9. Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552; Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.
10. Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787.
11. Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commn.* **2003**, 1560.
12. Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Chem. Commn.* **2002**, 2436.